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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	19

DATE MAILED: 10/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/723,713	SCHENK, DALE B.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this c mmunication appears n the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *33,34 and 56-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34 and 56-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17,18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 6/2/03 have been entered. Applicant's amendment added new claims 56-67. Therefore, claims 33-34, and 56-67 are pending and under examination. An action on the merits follows.

Please note that the Art Unit for examination of this application has changed. The new art unit is 1632. The examiner of record has also changed, see page 12 of the instant office action.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Priority

Applicant's amendment of the specification to contain a cross-reference to related applications is acknowledged. Based on the amendment to the specification and previous submittal of a new application data sheet, the office acknowledges that priority to the recited

applications under 35 U.S.C. 120 and 35 U.S.C. 119(e) is granted. Based on the parent applications to which priority is claimed, the effective filing date of the instant application is considered to be 12/2/97, which corresponds to the filing date of U.S. provisional application no. 60/067,740.

Drawings

The applicant's amendment of the brief description of the drawings section of the specification, and applicant's submission of amended Figures 11, 15A-E and 16 are acknowledged.

Information Disclosure Statement

The information disclosure statement filed 6/2/03, paper no. 18, fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the reference listed as citation number 304 states that the publication date is unknown. It has been placed in the application file, but the information referred to therein as pertains to reference no. 304 has not been considered as to the merits. It is noted that the applicant acknowledges that the date of public accessibility is not known for this document. While the applicant speculates that the grant proposal would not have been accessible before April 2, 1998, the applicant admits that the exact date of public accessibility is not known by the applicant. Further, please note that citation no. 144 listed in the IDS submitted on 10/9/01 was also not considered by the previous examiner of record. In the

absence of definitive information concerning the public accessibility of the information in the Raso grant, the relevance of any teachings therein cannot be determined.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 C(1).

Claim Rejections - 35 USC § 112

The rejection of claims 33-34 under 35 U.S.C. 112, first paragraph, for lack of written description is withdrawn.

The rejection of claims 33-34 under 35 U.S.C. 112, first paragraph, for lack of enablement is withdrawn. However, please note that claims 33-34 and new claims 56-67 are subject to new grounds of rejection under 35 U.S.C. 112, see below.

Claims 33-34 and 56-67 are **newly** rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention as claimed. The applicant's claims as written are drawn to methods of preventing or treating a disease characterized by amyloid plaques comprising Aβ peptide comprising administering a polynucleotide encoding a least one antibody chain to a patient wherein the antibody chain binds to an epitope within Aβ1-10, and is a chimeric, humanized, or human antibody chain.

The specification does not provide an enabling disclosure for chimeric, humanized, or human antibody chains comprising only a heavy or light chain, or the use of a single heavy or light chain gene or protein to bind to an epitope within Aβ1-10. The specification discloses the well known structural characteristics of antibodies on page 15. At the time of filing, it was known that antibodies are a tetrameric molecule comprising two heavy chains and two light chains. The applicant's claims as written are extremely broad and read on the use of a polynucleotide which encode only a single heavy or light chain gene. The binding domains of antibodies are located in the variable regions of the heavy and light chains. The close physical association of the heavy and light chain proteins in an antibody creates a three dimensional epitope binding domain specific for a particular peptide sequence presence in an antigen. The contributions of both the heavy and light chain variable regions are essential for epitope binding. The specification recognizes that both heavy and light chain variable regions are required to generate an antigen binding site. On page 15, lines 19-30, specifically discusses the need for both the heavy and light chain variable regions in forming the binding site. The specification does not provide any guidance for using only a heavy or light chain gene in the absence of the other, or provide any guidance or teachings

regarding single heavy or light chains which are capable of binding antigen, and specifically an epitope within the Aβ1-10 region of Aβ peptide. Therefore, based on the nature of the antibody binding domain which requires contributions from both the heavy and light immunoglobulin chains, the lack of guidance provided by the specification for heavy or light chains which by themselves are capable of binding the Aβ1-10 of Aβ peptide, and the breadth of the claims which reads on using polynucleotides which only encode a single immunoglobulin heavy or light chain, it would have required undue experimentation to practice the invention as claimed.

The specification fails to provide an enabling disclosure for preventing or treating diseases associated with amyloid plaques comprising Aβ peptide by administering a polynucleotide encoding a single chain, humanized, chimeric, or human antibody that binds to the Aβ1-10 region of Aβ peptide. The claims as written are broad and read on the administration of a "polynucleotide" encoding an antibody chain. The term polynucleotide encompasses DNA or RNA in the absence of any transcriptional regulatory regions, and also reads on various non-viral and viral expression vectors known in the art including plasmids, adenoviruses, retroviruses, herpes viruses, etc. The claims as written recite that following administration, the antibody chain is expressed in the patient. At the time of filing, it was well known that expression of a protein from a nucleic acid requires transcription and translation governed by regulatory elements present in the nucleic acid. Please note that the specification does not teach or suggest using messenger RNA. Such regulatory elements include promoters and enhancers. In the absence of these elements, the gene is not expressed. Based on the nature of gene expression and the breadth of the

claims, the skilled artisan at the time of filing would not have predicted success in expressing an encoded gene from a polynucleotide which is not operatively linked to transcriptional regulatory elements and as such undue experimentation would have been required to practice the instant invention as claimed. Please note that issues regarding the lack of enablement for the use of expression vectors encoding antibody chains are discussed in detail below.

Regarding claims 61 and 67, which recite that the antibody chain has the same binding specificity as antibody 10D5 or is in fact the 10D5 antibody. It is noted that the specification teaches that the 10D5 antibody binds to an epitope in the Aβ1-16 peptide. From the information provided, it is possible that the antibody recognizes only residues in Aβ11-16 or possibly a number of residues spanning Aβ1-16. The specification does not clarify whether the residues bound by the antibody are actually present in Aβ1-10 or whether the residues recognized by the antibody include Aβ11-16 residues. Therefore, it is unclear whether the 10D5 antibody or an antibody with the binding characteristics of the 10D5 antibody meets the claim limitations of claim 33 which state that the antibody chain binds to an epitope within Aβ1-10.

Regarding the step of "administering" the polynucleotide, the claims are broad and read on using any known route of administration and site of administration. While the specification does teach that systemic administration, such as intravenous, intraperitoneal, nasal, gastric, intradermal, intramuscular, subdermal infusion, or topical application can be used, the specification fails to provide an enabling disclosure for any of these routes of administration. The breadth of the term "polynucleotide" encoding an antibody was discussed above and stated to include numerous non-

viral and viral expression systems. The specification's working examples which utilize antibodies teach the administration of protein antibody and do not provide an exemplification of the administration of a polynucleotide encoding an antibody. The administration of protein antibody versus a polynucleotide encoding an antibody is substantially different. Direct administration of proteins allows for a definite dosage of the desired protein to be administered to a specific site. The administration of nucleic acid encoding a protein resulting in expression of the encoded protein is a far more complex and unpredictable process. Numerous factors complicate the therapeutic expression of genes, which have not been shown to be overcome by routine experimentations. These factors include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene statement and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, the site of administration and the disease being treated (Eck and Wilson, 1996, Goodman & Gilman's The pharmacological basis of therapeutics, Chapter 5, 77-101, in particular pages 81-82). The problems associated with known vector systems include inefficiency of target cell transfection/transduction, anti-vector host immune responses, and transiency of gene expression. Verma et al. teaches that," ... the lack of efficient delivery systems, lack of sustained expression,

and host immune reactions - remain formidable challenges" in gene therapy, and specifically identifies the "Achilles heel" of gene therapy as gene delivery (Verma et al. (1997) Nature, Vol. 389, page 239, column 1, paragraph 1, and column 3, paragraph 2).Verma points out that, " [t]here are considerable immunological problems to be overcome before adenoviral vectors can be used to deliver genes and produce sustained expression" and that the choice of an appropriate enhancer-promoter combination is critical to the level and consistency of gene expression from a particular vector - " .. [T]he search for such combinations is a case of trial and error for a given type of cell" (Verma et al. (1997) Nature, Vol. 389, page 240, column 2, paragraph 2, and column 3, line 1). Marshall et al. concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall et al. (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", that, "[m]ajor difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", and that "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol.." (Orkin et al. (1995) Report to the NIH, page 1, paragraphs 3-4, and page 8, paragraph 2). Thus, it is clear that at the time of filing, the skilled artisan would not have

considered the direct administration of nucleic acid for the therapy of disease as predictable. Therefore, based on the art-recognized unpredictability of achieving therapeutic levels of gene expression using currently available vectors at the time of filing, the limitation of the applicant's working examples to the administration of protein antibody and not nucleic acid encoding an antibody, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed.

Regarding applicant's submission of Arafat et al., the Arafat reference is post-filing reference published four years after applicant's effective filing date and as such does not demonstrate the state of the art at the time of filing. Further, the teachings of the Arafat et al. reference are distinct from the instant invention as claimed. Arafat et al. teaches the intravenous administration of an E1 deleted replication-defective adenovirus encoding a single chain antibody operably linked to a promoter. The single chain antibody disclosed binds to erbB-2 present on tumor cells. Arafat teaches that expression of the single chain antibody following intravenous adenoviral vector delivery resulted in inhibition of tumor growth of tumor cells injected subcutaneously. In contrast, the instant specification does not disclose the use of an E1 deleted replication incompetent adenoviral vector, the sole mention of adenoviruses appears on page 25 of the specification, and is not limited to the use of single chain antibodies. Further, the single chain antibody of Arafat recognizes a antigen present on tumor cells in the periphery and not in the brain. The ability of antibodies to bind to target antigens in the brain is negatively affected by the blood brain barrier which impedes antibody diffusion. In addition, the claims as written are

directed to the treatment of diseases associated with amyloid plaques, such as Alzheimer's disease which are substantially different from tumors and cancer. The applicant is also reminded that if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date. *In re Glass*, 181 USPQ 31, (CCPA 1974). Therefore, in view of the substantial differences between Arafat and the instant invention as claimed, the post-filing date of the Arafat reference, and the breadth of the claims, the disclosure of Arafat et al. does not support the enablement of the instant specification for the claims as written.

Regarding the declaration by Martin Koller, the declaratory data provided in the declaration relates to clinical trails using the Aβ protein itself and not an antibody or polynucleotide encoding an antibody which recognize Aβ peptide. While the purpose of administering the peptide is to generate antibodies, the mechanism of antibody generation and the nature of the antibodies created are substantially different from applicant's claimed invention which is drawn to administration of nucleic acids encoding the antibodies themselves. Antibodies generated following peptide immunization, a technique referred to as active immunization, are polyclonal and may bind numerous epitopes in the immunizing protein. In the instant invention, nucleic acid encoding a single monoclonal antibody is administered which binds to a specific epitope of the Aβ peptide. Therefore, due to the substantial differences between administration of

protein to generate antibodies and the direct administration of antibodies or nucleic acids encoding antibodies, a nexus cannot be found between the applicant's declaratory data and the instant claims as written.

The office has analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of the skilled artisan, and 8) the breadth of the claims, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement for claimed methods. Analysis of the combination of factors identified by Wands in light of the teachings of the specification led to the conclusion that the specification fails to provide sufficient guidance to enable the claims as written.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be

directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER